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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/990,185	PALCZEWSKI ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *23 August 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☒ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *1-27 and 30-36*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *See Continuation Sheet*

Jon Eric Angell

Continuation of 5. does NOT place the application in condition for allowance because: First, with respect to the request for reconsideration of the rejected claims, Applicants arguments have ben fully considered, but are not persuasive. It is respectfully pointed out that the instant claims are drawn to a targeting construct, a vector comprising said constrct, a cell comprising said construct, and a mouse whose genome comprises a functional disruption of one or BOTH rhodopsin gene alleles. As previously indicated the only contemplated use for the claimed targeting construct, vector and cell is to make the claimed mouse. However, since the claimed mouse is not enabled, the only contemplated use for the targeting construct, vector and cell is not enabled, thus the targeting construct, vector and cells themselves are also not enabled. A previous Office Action indicated that the contemplated uses for the claimed transgenic mouse is twofold: (1) for making large amounts of protein that can be purified (i.e., the transgenic mouse can be a bio-reactor for producing and purifying large amounts of the transgenic protein), and (2) as a model for drug screening assays. With respect to either of these contemplated uses for the transgenic animal, before one of skill in the art would be able use the claimed mouse (and thus the claimed targeting construct, vector and cells), one of skill in the art would have to be able to make the claimed mouse without having to perform an undue amount of additional experimentation. The claims are drawn to a mouse that expresses a transgene of interest in the rod outer segment (ROS) of the eye. However, the art or redord clearly indicates that it would not be a matter of routine experimentation to make the transgenic mouse encompassed by the claims without first performing an undue amount of additional experimentation. For instance, the claims clearly encompass making a transgenic animal wherein BOTH of the rhodopsin gene alleles have been functional disrupted. The specification describes using a specific targeting vector to specifically integrate the transgene of interest into the rhodopsin gene alleles by homologous recombination. Ryan et al. teaches that position effect is an important consideration with respect to making transgenic animals because insertion of the transgene could disrupt the expression of a critical gene. Although the specification and claims are drawn to methods of making a transgenic animal by homolgous recombination and not random integration, Ryan is still applicable because the claims encompass integrating the transgene specifically into the rhodopsin gene. The prioir art indicates that integration of a transgene into the rhodopsin genes causes developmental defects in the eye of the transgenic mouse, such that the ROS does not develop in a mouse whose rhodopsin gene has been functionally disrupted. As such, the position effect described by Ryan is applicable to the instant case because integration of the transgene such that the transgene causes the functional disruption of rhodopsin is a positional effect. Furthermore, Lem teaches that when BOTH alleles of rhodopsin are functionally inactivated (as is explicitly claimed) the ROS fails to form in these transgenic mouse. Since, the claims explicitly indicate that the transgene encodes a polypeptide comprising an ROS targeting signal operably associated with a rod-specific regulatory sequence, it is unpredictable how these animals wil express the transgene since the animal does not develop a ROS in its eye. Therefore, in order for one of skill in the art to be able to make and use the claimed invention, one of skill in the art would have to be able to make the claimed transgenic mouse that expresses the transgene of interest in the ROS or the transgenic mouse's eye. However, the prior art of record (Lem) clearly indicates that disrupting both alleles of the rhodopsin gene results in the failure of the ROS to form in the transgenic animals. Therefore, in order for one of skill in the art to be able to make and use the claimed invention, one of skill in the art would have to be able to make the claimed transgenic animal that expresses the transgenic gene of interest in the ROS of the eye without performing an undue amount of additional experimentation.

With respect to the teachings of Ryan et al., the applicants argue that the claimed flanking sequences avoid the deficiencies described by Ryan et al. (see p. 8, third paragraph of the response). In reply it is respectfully pointed out that Ryan teaches the importance of poistional effect, as indicated above, Therfore, although the instant invention does not utilize random integration, targeted homolgous recombination also has a positional effect in view of the teachings of Lem that functional disruption of the rhospdin gene results in the failure of the ROS to develop in the transgenic mouse. Therefore, Ryan is applicable to the instant case.

With respect to the Office's assertion that the invention requires the proper expression of the transgene in the ROS of the eye, applicants assert that they are not claiming all transgenic mice and has excluded those embodiments that fail to produce the transgenic polypeptide in the ROS (e.g., see p. 9 of the response). In reply it is respectfully pointed out that the issue is not whether or not the claims encompass transgenic mice that do and do not properly express the transgene in the ROS of the eye, but rather if the specification has provided enough guidance to be able to make a transgenic animal that does properly express the transgene of interest in the ROS of the transgenic mouse's eye. Considering the teachings of Lem, one of skill in the art would not be able to make the claimed transgenic mouse that properly expresses the transgene of interest in its ROS without performing an undue amnount of additional experimentation.

With respect to the teachings of Lem, applicants assert that Lem expressly describes the normal development of the retinas of rhodopsin-null mice by stating, "Retinas in mice lacking both rhodopsin alleles initially developed normally" (see p. 10-11). In reply, although Lem does indicate that the retinas of the transgenic mice "initially develop normally", Lem clearly teaches that the "ROS failed to form". As such although the retinas may intially develop normally, the ROS fails to form. As such it is unclear how the transgenic mouse could properly express the transgenic polypeptide in the ROS of the transgenic mouse when the ROS fails to form in the transgeinc mouse. The applicants also assert that Lem teaches a solution to overcome the lack of normal development of the retinas in rhodopsin knock-out mice. Specifically, it is asserted that Lem indicates that disruption of only a single rhodopsin gene results in the development of the retina with an ROS that had half the normal complement of rhodopsin with a slower degeneration. In reply, it is respectfully pointd out that the instant claims are not limited mice that have a disruption in a single rhosopsin allele. Furthermore, the claims explicitly claim a transgenic mouse that has BOTH rhodopsin alleles functionally disrupted. Therefore, applicants arguments are not persuasive.

With respect to the teachings of Holschneider, applicants assert that the Holschneider is inapplicable to the instant invention because Holschneider is concerned with observing changes in phenotype. In response, it is acknowledged that Holschneider is concerned with changes in phenotype. However, considering the instant claims involve the knocking out of the rhodopsin gene, Holschneider is applicable because Holschneider teaches that knocking out a gene can result in unexpected phrenotypes. Since the instant claims encompass a mouse that has a transgene inserted into the rhodopsion gene, thus knocking out the rhodopsin gene, any phenotype observed in the transgenic could be due to either the expression of the transgene or the knock-out of the rhodopsin gene. Therefore, Holschneider is applicable to the instant invention and applicants arguments are not persuasive.

With respect to the applicants assertion that the Office newly alleges that the transgenic mice described in the application lack a real world utility because there are less expensive alternative methods for producing the polypeptides of interest, it is respectfully pointed out that the instant claims are not rejected under 35 USC 101 for lacking utility. In order for a claimed invention to have utility, it must have one (1) substantial asserted utlity. It is acknowledged that there are two asserted utilities for the claimed invention: (1) for producing large amounts of protein for purification, and (2) for using the transgenic mouse as a model for drug screening assays. Since the second indicated asserted utility is sucbstantial, the claimed invention has utility and is not rejected under 35 USC 101. The submitted declaration has been considered, however, the submitted declaration only speaks to the credibility of the asserted utility for making and purifying large amounts of the polypeptide, and do not address the issues of whether or not an undue amount of additional experimentation would be required in order for one of skill in the art to be able to make and use the claimed invention. Therefore, the submitted declaration does not over come the rejection of claims under 35 USC 112, first paragraph.

Since applicants arguments and the submitted declaration has not overcome the rejection of claims under 35 USC 112, first paragraph, the claims stand finally rejected.

Continuation of 10. Other: The amendment received 8/23/04 merely cancels claims 28, 29, 37 and 38, which were previously withdrawn from consideration. As such, the proposed amendment has been entered, but does not overcoe any of the rejections of record..

DAVE T. NGUYEN
PRIMARY EXAMINER